PATENT COOPERATION TREATY

ANKOM

1999 -08- 30

PCT

From the INTERNATIONAL BUREAU

To:

ASTRA AKTIEBOLAG
Intellectual Property, Patents
S-151 85 Södertälje
SUÈDE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 23 August 1999 (23.08.99)	
Applicant's or agent's file reference H 2120-1 WO	**IMPORTANT NOTIFICATION**
International application No. PCT/SE99/00702	**International filing date** (day/month/year) 28 April 1999 (28.04.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
KING, Anne School of Biomedical Services The Worsley Building University of Leeds Leeds, LS2 9NQ United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
Please be advised of additional applicant/inventor for the US only.

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer P. Regis
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

002803821

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PCT/SE99/00702

PATENT COOPERATION TREATY

5640
09/381055

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

ASTRAZENECA AB
Intellectual Property, Patents
S-151 85 Södertälje
SUÈDE

5610

Date of mailing (day/month/year) 19 September 2000 (19.09.00)	
Applicant's or agent's file reference H 2120-1 WO	**IMPORTANT NOTIFICATION**
International application No. PCT/SE99/00702	**International filing date** (day/month/year) 28 April 1999 (28.04.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
DRAY, Andrew Astra Research Centre Montreal 7171 Frederick-Banting St. Laurent, Quebec H4S 1Z9 Canada	GB	CA
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
DRAY, Andrew AstraZeneca R&D Montreal 7171 Frederick-Banting St. Laurent, Quebec H4S 1Z9 Canada	GB	CA
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Ingrid Aulich
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

003532759

Copy for the Elected Office (EO/US)

PCT/SE99/00702

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

ASTRAZENECA AB
Intellectual Property, Patents
S-151 85 Södertälje
SUÈDE

Date of mailing (day/month/year)
19 September 2000 (19.09.00)

Applicant's or agent's file reference
H 2120-1 WO

IMPORTANT NOTIFICATION

International application No.
PCT/SE99/00702

International filing date (day/month/year)
28 April 1999 (28.04.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address
CABERO, José, Luis
Astra Hässle AB
S-431 83 Mölndal
Sweden

State of Nationality: SE
State of Residence: SE
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
CABERO, José, Luis
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden

State of Nationality: SE
State of Residence: SE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Ingrid Aulich

Telephone No.: (41-22) 338.83.38

QL 09/381055 50 CO (11-08-)

PERATION TRE

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 20 January 2000 (20.01.00)	
International application No. PCT/SE99/00702	**Applicant's or agent's file reference** H 2120-1 WO
International filing date (day/month/year) 28 April 1999 (28.04.99)	**Priority date** (day/month/year) 28 April 1998 (28.04.98)
Applicant ASGHAR, Aziz et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

26 November 1999 (26.11.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer R. E. Stoffel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

5600

Copy for the Elected Office (EO/US)

PCT/SE99/00702

PATENT COOPERATION TREATY

09/381055

PCT

From the INTERNATIONAL BUREAU

To:

ASTRAZENECA AB
Intellectual Property, Patents
S-151 85 Södertälje
SUÈDE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 04 April 2000 (04.04.00)	
Applicant's or agent's file reference H 2120-1 WO	**IMPORTANT NOTIFICATION**
International application No. PCT/SE99/00702	**International filing date** (day/month/year) 28 April 1999 (28.04.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
ASTRA AKTIEBOLAG S-151 85 Södertälje Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
ASTRAZENECA AB S-151 85 Södertälje Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
Please be advised that the above change also refers to the name indicated in Box No. IV of the request form.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer P. Regis
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

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16

PATENT COOPERATION TREATY

PCT

REC'D 22 AUG 2000

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
H 2120-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE99/00702	28.04.1999	28.04.1998
International Patent Classification (IPC) or national classification and IPC7		
A 61 K 31/165		
Applicant		
AstraZeneca AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.11.1999	01.08.2000
Name and mailing address of the IPEA/SE	Authorized officer
Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Solveig Gustavsson/gh Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/00702

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☐ the international application as originally filed.

☒ the description, pages 1-11, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-12, filed with the letter of 21.07.2000,
Nos. _____, filed with the letter of _____.

☒ the drawings, ~~sheets~~/fig 1-6, as originally filed,
~~sheets~~/fig _____, filed with the demand
~~sheets~~/fig _____, filed with the letter of _____,
~~sheets~~/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/00702

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-2,9-11

because:

☒ the said international application, or the said claims Nos. 9
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-2,9-11
are so unclear that no meaningful opinion could be formed *(specify)*:

see extra sheet

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been establised for said claims Nos. _____

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

Present claims 1-2, 9 and 10-11 relate to a compound/method defined by reference to desirable characteristic, namely NMDA antagonist activity or sodium antagonist activity. The claims cover all compounds having this characteristic, whereas the application provides support within the meaning of Article 6 PCT and /or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the applications so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. As the search has been limited mainly to those compounds mentioned in the claims or the description, a complete opinion regarding novelty and inventive step cannot be established.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/00702

V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-9	YES
	Claims	10-12	NO
Inventive step (IS)	Claims	1-9	YES
	Claims	10-12	NO
Industrial applicability (IA)	Claims	1-8,10-12	YES
	Claims	9	NO

2. Citations and explanations

The claimed invention relates to the use of NMDA-antagonists for treatment of irritable bowel syndrome (IBS) and to pharmaceutical compositions comprising a compound having NMDA receptor antagonistic properties.

WO 97/09317 A2 shows compounds that can be used for treatment of irritable bowel syndrome.
However, the compounds known from this document differ structurally from the exemplified compounds of the present application. Neither are these compounds referred to as NMDA receptor antagonists.
Therefore, the subject matter of claims 1-9 is considered to have novelty and inventive step.

Claims 10-12 relate to pharmaceutical compositions comprising a compound having NMDA receptor antagonistic properties. Such compositions are known from WO 97/14415 A1.
Also pharmaceutical compositions containing the compound of formula I, are known from EP 279937 A, cited in the application.
Thus claims 10-12 are considered to lack novelty and inventive step.
However, claims to a known pharmaceutical preparation for use in a new medical treatment are allowed in at least one country.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

Present claims 1-2, 9 and 10-11 relate to a compound/method defined by reference to desirable characteristic, namely NMDA antagonist activity. The claims cover all compounds having this characteristic, whereas the application provides support within the meaning of Article 6 PCT and /or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support for the whole area of the claimed scope. Independent of the above reasoning, the claims lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved.

Therefore, claims 1-2 (and also claims 10-11 in some countries) cannot be allowed with their present broad formulation.

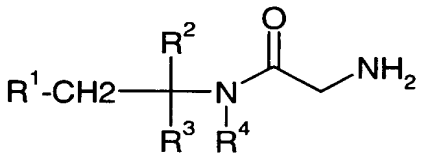
Claim 9 is directed to use of a compound for the treatment of a medical disorder.
For the assessment of the aforesaid claims on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims.
Most countries do not recognise as industrially applicable the subject-matter of claim directed to treatment of medical disorders or to the use of a compound in medical treatment. However, they will allow, claims to a known compound for first use in medical treatment (first medical indication) and the use of such a compound for the manufacture of a medicament for a new medical treatment (second medical indication).

CLAIMS

1. Use a compound having NMDA receptor antagonist activity in the manufacture of a medicament for the treatment of irritable bowel syndrome (IBS).

2. Use according to claim 1 wherein the compound having NMDA receptor antagonist activity is a non-competitive NMDA receptor antagonist.

3. Use according to claim 1 wherein the compound having NMDA receptor antagonist activity is a compound of formula (I):



(I)

where:

R^1 and R^2 are independently phenyl or 4-fluorophenyl;

R^3 is hydrogen, C_{1-6} alkyl or methoxycarbonyl;

R^4 is hydrogen or methyl;

and metabolites and isomers thereof both as a free base and pharmaceutically acceptable salts thereof.

4. Use according to claim 3 wherein the compound of formula (I) is remacemide or a pharmaceutically acceptable salt thereof.

5. Use according to claim 3 wherein the compound is 2,3-diphenyl-2-propylamine or a pharmaceutically acceptable salt thereof.

6. Use according to claim 3 wherein the compound is (S)-1-phenyl-2-(2-pyridyl)ethanamine or a pharmaceutically acceptable salt thereof.

7. Use according to claim 1 wherein the NMDA receptor antagonist is memantine or a pharmaceutically acceptable salt thereof.

8. Use according to claim 1 where the compound is 2-amino-N-(1,2-diphenylethyl)acetamide, alpha-phenyl-1H-pyrazole-1-ethanamine, (+)-N-ethyl-1-phenyl-

2-(3-pyrazine)ethanamine, or 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine or a pharmaceutically acceptable salt thereof.

9. A method of treating or preventing irritable bowel syndrome which comprises administering to a patient in the need thereof a compound having NMDA receptor antagonist activity or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition for the treatment of irritable bowel syndrome comprising a compound having NMDA receptor antagonist activity and a pharmaceutical acceptable carrier.

11. Pharmaceutical composition according to claim 10, wherein the compound having NMDA receptor antagonist activity is a non-competitive NMDA receptor antagonist.

12. Pharmaceutical composition according to claim 10, wherein the compound having NMDA receptor antagonist activity is a compound of formula I defined in claim 3.

09/381055

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/165, 31/13, 31/41, 31/44, 31/495

A1

(11) International Publication Number: **WO 99/55323**

(43) International Publication Date: 4 November 1999 (04.11.99)

(21) International Application Number: PCT/SE99/00702

(22) International Filing Date: 28 April 1999 (28.04.99)

(30) Priority Data:

9801494-7	28 April 1998 (28.04.98)	SE
9803954-8	18 November 1998 (18.11.98)	SE

(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ASGHAR, Aziz [GB/GB]; School of Biomedical Sciences, The Worsley Building, University of Leeds, Leeds LS2 9NQ (GB). CABERO, José, Luis [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). DRAY, Andrew [GB/CA]; Astra Research Centre Montreal, 7171 Frederick-Banting, St. Laurent, Quebec H4S 1Z9 (CA). KING, Anne [GB/GB]; School of Biomedical Services, The Worsley Building, University of Leeds, Leeds, LS2 9NQ (GB).

(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).

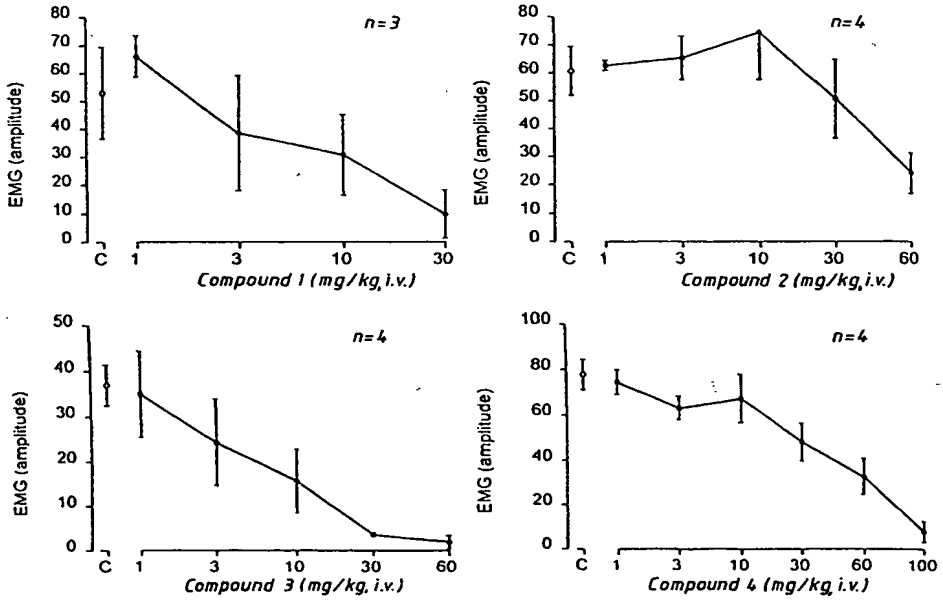
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: USE OF NMDA ANTAGONISTS FOR TREATMENT OF IRRITABLE BOWEL SYNDROME



(57) Abstract

The invention relates to the use of pharmaceutical compounds having NMDA antagonist activity for treating certain conditions in the gastrointestinal tract, such as functional gastrointestinal disorders, and in particular irritable bowel syndrome (IBS). The invention also relates to pharmaceutical compositions to be used in the treatment of IBS and product comprising such compounds and a pharmaceutical acceptable carrier.

PCT

REQUEST

SEP 199

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* H 2120-1 WO

Box No. I TITLE OF INVENTION

NOVEL USE

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Astra Aktiebolag
S-151 85 Södertälje
Sweden

☐ This person is also inventor.

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.

State *(that is, country)* of nationality: SE

State *(that is, country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ASGHAR, Aziz
School of Biomedical Sciences
The Worsley Building
University of Leeds
Leeds LS2 9NQ
United Kingdom

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is,country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Intellectual Property, Patents
Astra Aktiebolag
S-151 85 Södertälje
Sweden

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.

☐ **Adress for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CABERO, José Luis
Astra Hässle AB
S-431 83 Mölndal
Sweden

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: SE

State *(that is, country)* of residence: SE

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DRAY, Andrew
Astra Research Centre Montreal
7171 Frederick-Banting
St: Laurent
Quebec H4S 1Z9
Canada

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: CA

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

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item (1) (28.04.98) 28 April 1998	9801494-7	Sweden		
item (2) (18.11.98) 18 November 1998	9803954-8	Sweden		
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21 December 1998	ITS SE98/00387	Sweden

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	4
description (excluding sequence listing part)	:	11
claims	:	2
abstract	:	1
drawings	:	5
sequence listing part of description	:	
Total number of sheets	:	23

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
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Figure of the drawings which should accompany the abstract: 3

Language of filing of the international application: English

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Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Södertälje, 28 April 1999

Birgitta Larsson

Birgitta Larsson
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(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S–151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ASGHAR, Aziz [GB/GB]; School of Biomedical Sciences, The Worsley Building, University of Leeds, Leeds LS2 9NQ (GB). CABERO, José, Luis [SE/SE]; Astra Hässle AB, S–431 83 Mölndal (SE). DRAY, Andrew [GB/CA]; Astra Research Centre Montreal, 7171 Frederick–Banting, St. Laurent, Quebec H4S 1Z9 (CA). KING, Anne [GB/GB]; School of Biomedical Services, The Worsley Building, University of Leeds, Leeds, LS2 9NQ (GB).

(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S–151 85 Södertälje (SE).

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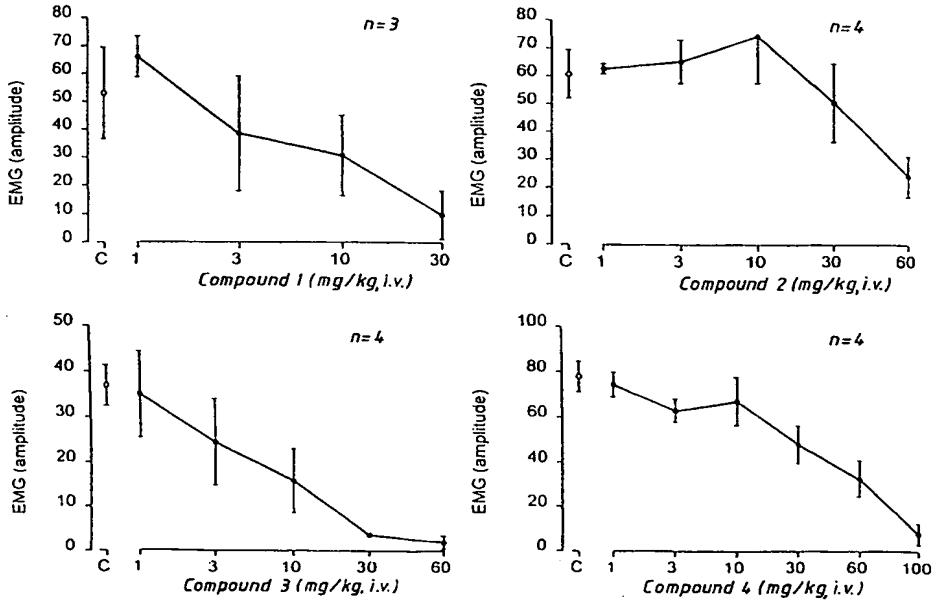
(54) Title: USE OF NMDA ANTAGONISTS FOR TREATMENT OF IRRITABLE BOWEL SYNDROME



(57) Abstract

The invention relates to the use of pharmaceutical compounds having NMDA antagonist activity for treating certain conditions in the gastrointestinal tract, such as functional gastrointestinal disorders, and in particular irritable bowel syndrome (IBS). The invention also relates to pharmaceutical compositions to be used in the treatment of IBS and product comprising such compounds and a pharmaceutical acceptable carrier.

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USE OF NMDA ANTAGONISTS FOR TREATMENT OF IRRITABLE BOWEL SYNDROME

Field of the invention

The present invention relates to the use of compounds having NMDA antagonist activity for treating certain conditions in the gastro intestinal tracts, such as functional gastrointestinal disorders, and in particular irritable bowel syndrome (IBS), where the condition known as visceral hypersensitivity may be a major contributory factor in the observed symptoms. The invention also relates to pharmaceutical compositions intended for the treatment of IBS.

Background of the invention

Compounds having NMDA (N-methyl-D-aspartate) antagonist activity are known in the art, for example see Watkins et al., Trends in Pharmacological Science, 11:25, 1990.

In particular certain compounds are disclosed in EP-A 279937 as having NMDA antagonist activity and are useful for treating various CNS disorders such as epilepsy and Parkinson's disease. In particular the compound known as remacemide is known from EP-A 279937 as an NMDA antagonist and has also been shown to act as a sodium channel antagonist (Wamil et al., Epilepsy Research 23:1. 1996). It has now surprisingly been found that antagonists of the NMDA receptor have an attenuating effect on the visceromotor response to colorectal distention in rats when dosed intravenously but not when dosed intrathecaly. This observation coupled with the observation that the compounds also show an attenuating effect in a model of pelvic nerve afferent activity, would suggest that the effect of these NMDA antagonists is dependant at least in part on a peripheral component. It does not however, rule out an additional action at the spinal or supra-spinal level, in the attenuation of the response to colorectal distension . As a result it is expected that compounds having NMDA antagonist activity which in some cases may be combined with sodium channel antagonist activity will be useful for the treatment of certain conditions in the gastro intestinal tracts where the phenomenon of visceral hypersensitivity may be involved, such as functional bowel disorders, and in particular irritable bowel syndrome.

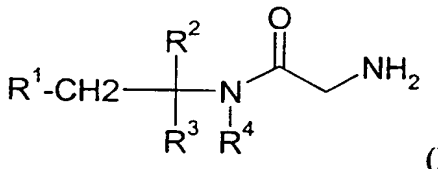
Suitable NMDA antagonists include those listed in WO 94/13295 such as a) channel blockers, i.e. antagonists which operate in an uncompetitive or non-competitive manner to block the NMDA receptor channel, b) receptor antagonists that compete with NMDA to act at the NMDA binding site, c) agents acting at either the glycine co-agonist site or any of the several modulation sites such as the zinc site, the magnesium site, the redox

modulatory site, or the polyamine site, d) agents which inhibit the downstream effects of NMDA receptor stimulation such as agents which inhibit the activation of protein kinase C activation by NMDA stimulation, antioxidants, and agents that decrease phosphatidylinositol metabolism.

The hypersensitive state, such as that which may occur in patients with functional bowel disorders, may occur as a result of excessive receptor activation. Hence, antagonists which operate in an uncompetitive or non-competitive manner, may offer an advantage as they can only block the receptor when it is in its activated state and not when it is in its non-activated form. Thus excess receptor activity will be curtailed.

Examples of preferred compounds useful for the invention include but are not limited to memantine (Merz) and remacemide and their metabolites

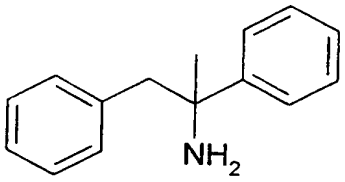
Particularly suitable compounds are those disclosed in EPA 279937, such as a compound of formula (I):



(I)

where:
R^1 and R^2 are independently phenyl or 4-fluorophenyl;
R^3 is hydrogen, C_{1-6} alkyl or methoxycarbonyl;
R^4 is hydrogen or methyl;
and metabolites and isomers thereof both as free base and pharmaceutically acceptable salts thereof.

Preferred compounds of formula (I) include 2-amino-N-(1,2-diphenyl-1-methylethyl)acetamide (remacemide) or a metabolite thereof, such as the compound 2,3-diphenyl-2-propylamine or a pharmaceutically acceptable salt thereof which has the following structure:



Other preferred compounds include those disclosed in WO 93/20052, in particular (S)-1-phenyl-2-(2-pyridyl)ethanamine as well as the compounds mentioned in the experimental section herein. Certain compounds mentioned herein are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these individual stereoisomeric forms and to any mixtures thereof including racemates. The invention also extends to any tautomeric forms of the compounds mentioned and mixtures thereof.

Suitable salts of the above noted compounds include all known pharmaceutically acceptable salts such as acid addition salts and preferably hydrochloride salts.

Compounds which possess anti-inflammatory properties are useful in the prevention of clinical hyperalgesia and other pathologies associated with chronic pain such as neuropathies and joint inflammation. Particular inflammatory disorders which can be treated include arthritic conditions, eczema, psoriasis, dermatitis and other inflammatory conditions such as sunburn; inflammatory eye conditions such as uveitis and conjunctivitis; lung disorders in which inflammation is involved such as asthma and bronchitis; conditions of the GI tract including aphthous ulcers, gingivitis, Crohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional iletis, peptic ulceration, IBS, pyresis, pain, including inflammatory induced pain, and other damage to the GI tract, for example damage from infections by, for example, Helicobacter pylori, or undesirable side effects from treatments with non-steroidal anti-inflammatory drugs.

Outline of the invention

In a preferred embodiment it has been found that certain NMDA antagonists are expected to be useful for the treatment of certain conditions in the GI tract, in particular functional bowel disorders.

In a further aspect the invention therefore provides use of an NMDA antagonist for the treatment or prevention of irritable bowel syndrome (IBS). Suitable NMDA antagonists

include those listed above. In particular a preferred aspect of the invention relates to the use of non-competitive NMDA antagonists such as memantine for the treatment of IBS. Other preferred compounds for the treatment or prevention of IBS include remacemide, and also compounds of formula I, such as (S)-1-phenyl-2-(2-pyridyl)ethanamine, 2-amino-N-(1,2-diphenylethyl)acetamide hydrochloride, alpha-phenyl-1H-pyrazole-1-ethanamine hydrochloride, (+)-N-ethyl-1-phenyl-2-(3-pyrazine)ethanamine hydrochloride and 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride.

In a preferred embodiment the invention provides a method of treating or preventing IBS which comprises administering to a patient in the need thereof a compound having NMDA antagonist activity or a pharmaceutically acceptable salt thereof.

The invention also provides the use of a compound having NMDA antagonist activity in the manufacture of a medicament for use in the prevention or treatment of IBS, and a pharmaceutical composition comprising such a compound and a pharmaceutical acceptable carrier.

Other diseases which may be treated with the compounds of the invention include functional gastrointestinal disorders as defined by the Rome group in *"The Functional Gastrointestinal Disorders"*, D. Drossman ed., Little Brown & Co., 1994, p.p. 370. In particular: irritable bowel syndrome and functional dyspepsia (non-ulcer dyspepsia) but also functional chest pain of presumed oesophageal origin, functional heartburn, functional dysphagia, non-cardiac chest pain, symptomatic gastro-oesophageal disease, gastritis, aerophagia, functional constipation, functional diarrhea, burbulence, chronic functional abdominal pain; functional biliary pain, functional incontinence, functional ano-rectal pain, pelvic floor dyssenergia, un-specified functional ano-rectal disorder. Additional conditions include cholecystalgia, interstitial cystitis, dysmenorrhea, dyspareunia, cancer related pain, migraine, osteoarthritis and rheumatoid arthritis.

Use of the invention

Suitable daily dose ranges of the compound having NMDA antagonist activity are from about 1.0 mg/kg to about 100 mg/kg. Unit doses may be administered conventionally once or more than once a day, for example, 2, 3, or 4 times a day, more usually 1 or 2 times a day.

The following examples illustrate the invention.

Example 1

Effects of non-competitive NMDA glutamate receptor antagonists on the visceromotor response (VMR) elicited by colorectal distension (CRD)

Methods:

Animals

Adult male Sprague-Dawley rats (250-350g, Harlan, San Diego, CA) served as animal subjects. Rats were housed 5-6 per cage, allowed free access to food and water, and were maintained on a 12 h light-dark cycle (lights on between 06.00 and 18.00 h).

Surgical preparation

Rats were deeply anesthetized with pentobarbital sodium (45 mg/kg, Nembutal, Abbott Labs, North Chicago, IL) administered intraperitoneally. Electrodes (Teflon coated stainless steel wire, Cooner Wire Sales, Chatworth, CA) were stitched into the external oblique musculature, just superior to the inguinal ligament, for electromyographic (EMG) recording. The electrode leads were tunneled subcutaneously and exteriorized at the nape of the neck for future access. Some animals were also implanted with venous catheters in the femoral vein to enable i.v. administration of drugs. For intrathecal (i.t.) drug administration, an i.t. catheter (PE-10 tubing, 8.5 cm long) was inserted through the dura overlying the atlanto-occipital junction and threaded to the level of the lumbar enlargement (Yaksh and Rudy, 1976). The venous or i.t. catheter was surgically anchored to musculature at the back of the neck, and externalized with the electrode leads. The wounds were closed in layers with 4-0 silk. Rats were housed singly and allowed to recuperate for at least 3-5 days prior to testing.

Behavioral testing

The stimulus employed has been previously described (Gebhart and Sengupta, 1996). Briefly, the descending colon and rectum were distended by pressure-controlled air inflation of a 6 cm long flexible latex balloon tied around a flexible tube (Tygon). The balloon was lubricated (Surgilube, E. Fougera and Co., Melville, NY), inserted intra-anally

and anchored by taping the balloon catheter to the base of the tail. Noxious phasic CRD (80 mmHg, 20 s) was achieved with the aid of a device (developed in house at Astra Hässle.) Intracolonic pressure was continuously monitored on line. The behavioral response quantified was the visceromotor response, a contraction of the abdominal and hindlimb (Ness and Gebhart, 1988). EMG activity in the external oblique musculature was quantified by computing the average amplitude (Dr. Alfred Bayati Astra Hässle). Each distension trial lasted 60 s and EMG activity was quantified 20 s before distension (baseline), during distension, and 20 s after distension. The increase in EMG amplitude during distension over baseline was recorded as the response.

Experimental protocol

On the day of testing, animals were briefly anesthetized with Metophane®, and the balloon was inserted and secured in place as described above. Rats were allowed to recover for 30-40 min, following which two stable control responses to CRD (80 mmHg, 20 s, 4 min interstimulus interval) were obtained.

Drugs were administered i.v. into the femoral vein through the indwelling catheter. All doses were administered in a volume of up to 230 µl followed by a flush with 100 µl of preservative-free saline over a period of 30s. Dose response curves were generated using a cumulative dosing paradigm. The first i.v. injection was made 2 min after the second control response. Subsequent doses were injected 8 min apart, thus allowing two distensions after each dose. Data are reported as the average response to the two distensions.

In one group of animals, memantine was administered to the lumbar enlargement through the indwelling i.t. catheter with the aid of a 16 gauge injection needle connected to a 25 µl Hamilton syringe by a length of polyethylene tubing (PE-10). All doses were administered in a volume of 5 µl followed by a flush with 10 µl of preservative-free saline over a period of 1 min. The progress of the injection was continuously monitored by following the movement of an air bubble in the tubing. The dose response curve was generated using a cumulative dosing paradigm. The first i.t. injection was made 2 min after the second control response. Subsequent doses were injected 8 min apart, thus allowing two distensions after each dose. Data are reported as the average response to the two distensions.

Drugs

Drugs used in the present study were memantine hydrochloride (Research Biochemicals International, Natick, MA), and 2-amino-N-(1,2-diphenylethyl)acetamide hydrochloride, alpha-phenyl-1H-pyrazolc-1-ethanamine hydrochloride, (+)-N-ethyl-1-phenyl-2-(3-pyrazine)ethanamine hydrochloride and 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride (Astra Arcus, Rochester, NY). Stock solutions were freshly prepared by dissolving the drugs in distilled water, and then diluted as needed.

Results:

All drugs administered i.v. produced a dose-dependent attenuation of the VMR to noxious CRD (80 mmHg) in naïve animals without producing any apparent motor effects. At the most effective dose tested, memantine (10 mg/kg) attenuated the VMR to 28 % of control, 2-amino-N-(1,2-diphenylethyl)acetamide hydrochloride (60 mg/kg) to 40 % of control, alpha-phenyl-1H-pyrazole-1-ethanamine hydrochloride (100 mg/kg) to 10 % of control, (+)-N-ethyl-1-phenyl-2-(3-pyrazine)ethanamine hydrochloride (60 mg/kg) to 5 % of control and 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride to 13 % of control.

In contrast, memantine administered i.t. (1-100 nmol) was without effect in diminishing the VMR to CRD. This is supported by other studies wherein NMDA receptor antagonists administered i.t. were without effect on normal visceral nociceptive reflexes, except in doses that produce motor impairment (Rice and McMahon, 1994; Coutinho et al., 1996a; Ide et al., 1997).

These data suggest that memantine as well as the other open channel blockers tested may be interacting with peripheral NMDA receptors.

Therefore it appears that activity at peripheral NMDA receptors plays a role in modulating responses to CRD.

Results are presented in Figures 1 to 4, which figures show the following:

Fig 1. Illustrates the effect of intravenous (i.v.) administration of memantine hydrochloride on viscero-motor responses (VMR) to noxious colorectal distension of concious rats. Memantine dose-dependantly attenuate VMR when given i.v. from 1-10 mg/kg.

Fig 2. Effect of intrathecal (i.t.) administration of memantine hydrochloride on viscero-motor responses (VMR) to noxious colorectal distension of concious rats. Memantine did not attenuate VMR when given i.t. up to a dose of 100 nmol.

Fig 3. Effect of intravenous (i.v.) administration of four compounds on viscero-motor responses (VMR) to noxious colorectal distension of concious rats. All four compounds dose-dependently (1-10 mg/kg) attenuated VMR.
Compound 1 is 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride
Compound 2 is 2-amino-N-(1,2-diphenylethyl)acetamide hydrochloride
Compound 3 is (+) N-ethyl-1-phenyl-2-(3-pyrazine)ethanamine hydrochloride
Compound 4 is alpha-phenyl-1H-pyrazole-1-ethanamine hydrochloride

Fig 4. Effect of intrathecal (i.t.) administration of three compounds on viscero-motor responses (VMR) to noxious colorectal distension of concious rats. None of the three compounds attenuated VMR up to a dose of 300nmol.
Compound 1 is 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride
Compound 2 is 2-amino-N-(1,2-diphenylethyl)acetamide hydrochloride
Compound 4 is alpha-phenyl-1H-pyrazole-1-ethanamine hydrochloride

Example 2

Effects of non-competitive NMDA glutamate receptor antagonists on pelvic afferent nerve activity

General procedures: Male *S*prague-Dawley rats 425-450 g) were anesthetized initially with sodium pentobarbital (40-45 mg/kg ip) and maintained with α-chloralose (60 mg kg^{-1} h^{-1}). The trachea was cannulated for mechanical ventilation with room air. The left common carotid artery was cannulated for recording blood pressure. The femoral artery and vein were catheterized for injection of drug and anesthetic, respectively. Rats were paralyzed with pancuronium bromide (0.3 mg/kg i.v.) and ventilated with room air (55-60 strokes/min and 3-4 ml stroke volume). Supplemental doses of pancuronium bromide (0.2-

0.3 mg kg^{-1} h^{-1}) were given to maintain paralysis during the course of experiment. The mean arterial blood pressure was monitored continuously and maintained at >80 mm Hg with supplemental intravenous injection of 5% dextrose in saline given in a bolus of 1 to 1.5 ml as required. The core body temperature was maintained at 36°C by a hot-water-circulating heating pad underneath the rat and a feedback-controlled heat lamp (thermoprobe inserted into the thoracic esophagus). At the end of an experiment, the rat was killed by an overdose of intravenous pentobarbital sodium.

Surgical procedure: The lower abdomen was exposed by a 3-4 cm long incision laterally at the left flank. The urinary bladder was emptied and catheterized (PE-100) through the fundus. The urethra was ligated close to its entry to the penis and urine was constantly evacuated via the fundic catheter.

The pelvic nerve was approached near the major pelvic ganglion and isolated. A pair of Teflon-coated stainless steel wires stripped at the tips were wrapped around the pelvic nerve and sealed with non-reactive Wacker gel. The hypogastric, pudendal, and femoral nerves were isolated and transected. The sciatic nerve was approached through the ischiatic notch and transected. The abdomen was closed with silk sutures.

The lumbosacral spinal cord was exposed by laminectomy (T_{13}-S_2) and the rat was suspended from thoracic vertebral and ischial spinal clamps. The dorsal skin was reflected laterally and tied to make a pool for mineral oil. The dura was carefully removed and the spinal cord was covered with warm (37°C) mineral oil. For colorectal distension (CRD), a 6 - 7-cm long, 2 - 3 cm diameter flaccid, flexible latex balloon was inserted into the descending colon and rectum as described above.

Recordings of afferent nerve action potentials: The S_1 dorsal root was identified and decentralized at its entry to the spinal cord. Recordings were made from the distal cut end of the central processes of primary afferent fibers. a length of nerve fiber was draped over a black micro-base plate immersed in warm (37°C) mineral oil. The dorsal rootlet was split into thin bundles and a fine filament was isolated from the bundle to obtain a single unit. Electrical activity of single units was recorded monopolarly by placing a teased fiber over one arm of a bipolar silver-silver chloride electrode; a fine strand of connective tissue was placed across the other pole of the electrode. Action potentials were monitored continuously by analog delay and displayed on a storage oscilloscope after initial amplification through a low-noise ac differential amplifier. Action potentials were processed through a window discriminator and the frequency of impulses were counted (1s binwidth) on-line using the spike2/ced 1401 data acquisition program. Peri-stimulus time

histograms (PSTH), urinary bladder or colonic distending pressures, and blood pressure were displayed on-line.

Experimental protocol: Pelvic nerve input to the s_1 dorsal root was identified first by electrical stimulation of the pelvic nerve (a single 0.5 ms square-wave pulse at 5-8 mA). The organ innervated was identified by response to phasic CRD (80mm Hg, 2-3s). If a fiber responded to CRD, a stimulus-response function to phasic distending pressures of 5, 10, 20, 30, 40, 60, 80, and 100 mm Hg, 30s each at 4 min intervals was determined.

The effect of the NMDA-antagonist, memantine, was tested on responses of mechanosensitive pelvic nerve afferents to 80 mm Hg of CRD. The drug was administered intra-arterially in a cumulative dose paradigm. Each dose of the drug was given 2 min before CRD. A cumulative dose-response relationship for memantine was obtained by giving 1, 3, 6 and 10 mg/kg.

Figure 5 shows the results for memantine and Figure 6 shows the corresponding results with 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine.

Results and conclusion: Intra-arterially injected memantine reduced, in a dose-dependent fashion, the pelvic nerve activity elicited by distention of the colon (80 mm Hg), as can be seen from Figure 5.

The observations hereby provided are consistant with a model in which the non-competitive NMDA-antagonist memantine reduces the pelvic nerve activity elicited by colorectal distention by a peripheral mechanism of action.

The data shown in Figure 6 was obtained when the experiment was repeated with 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine.

References:

Coutinho S.V., Meller S.T. and Gebhart, G.F. (1996a) Intracolonic zymosan produces visceral hyperalgesia in the rat that is mediated by spinal NMDA and non-NMDA receptors. *Brain Res.* 736, 7-15.

Coutinho, S.V., Urban, M.O. and Gebhart, G.F.(1996b) NMDA and non-NMDA receptors in the RVM modulate responses to colorectal distension from the inflamed colon. In: Abst. 8th World Cong. on Pain, pg.251, IASP Press, Seattle, WA.

Gebhart, G.F. and Sengupta, J.N. (1996) Evaluation of visceral pain. In *Handbook of Methods in Gastrointestinal Pharmacology* (ed. Gaginella, T.S.), pp. 359-374, CRC Press, Boca Raton.

Ide, Y., Maehara, Y., Tsukahara, S., Kitahata, L.M. and Collins, J.G. (1997) The effects of an intrathecal NMDA receptor antagonist (AP5) on the behavioral changes induced by colorectal inflammation with turpentine in rats. *Life Sci.* **60**, 1359-1363.

Ness T.J. and Gebhart, G.F. (1988) Colorectal distension as a noxious visceral stimulus: physiologic and pharmacologic characterization of pseudaffective reflexes in the rat. *Brain Res.* **450,** 153-169.

Rice, A.S.C. and McMahon, S.B. (1994) Pre-emptive intrathecal administration of an NMDA receptor antagonist (AP5) prevents hyper-reflexia in a model of persistent visceral pain. *Pain* **57**, 335-340.

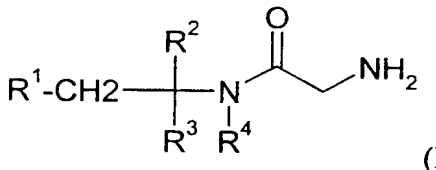
Yaksh, T.L. and Rudy, T.A. (1976) Chronic catheterization of the spinal subarachnoid space. *Physiol. Behav.* **17**, 1031-1036.

CLAIMS

1. Use a compound having NMDA antagonist activity in the manufacture of a medicament for the treatment of irritable bowel syndrome (IBS).

2. Use according to claim 1 wherein the compound having NMDA antagonist activity is a non-competitive NMDA antagonist.

3. Use according to claim 1 wherein the compound having NMDA antagonist activity is a compound of formula (I):



(I)

where:

R^1 and R^2 are independently phenyl or 4-fluorophenyl;

R^3 is hydrogen, C_{1-6} alkyl or methoxycarbonyl;

R^4 is hydrogen or methyl;

and metabolites and isomers thereof both as a free base and pharmaceutically acceptable salts thereof.

4. Use according to claim 3 wherein the compound of formula (I) is remacemide or a pharmaceutically acceptable salt thereof.

5. Use according to claim 3 wherein the compound is 2,3-diphenyl-2-propylamine or a pharmaceutically acceptable salt thereof.

6. Use according to claim 3 wherein the compound is (S)-1-phenyl-2-(2-pyridyl)ethanamine or a pharmaceutically acceptable salt thereof.

7. Use according to claim 1 wherein the NMDA antagonist is memantine or a pharmaceutically acceptable salt thereof.

8. Use according to claim 1 where the compound is 2-amino-N-(1,2-diphenylethyl)acetamide, alpha-phenyl-1H-pyrazole-1-ethanamine, (+)-N-ethyl-1-phenyl-

2-(3-pyrazine)ethanamine, or 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine or a pharmaceutically acceptable salt thereof.

9. A method of treating or preventing irritable bowel syndrome which comprises administering to a patient in the need thereof a compound having NMDA antagonist activity or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition for the treatment of irritable bowel syndrome comprising a compound having NMDA antagonist activity and a pharmaceutical acceptable carrier.

11. Pharmaceutical composition according to claim 10, wherein the compound having NMDA antagonist activity is a non-competitive NMDA antagonist.

12. Pharmaceutical composition according to claim 10, wherein the compound having NMDA antagonist activity is a compound of formula I defined in claim 3.

Fig. 1

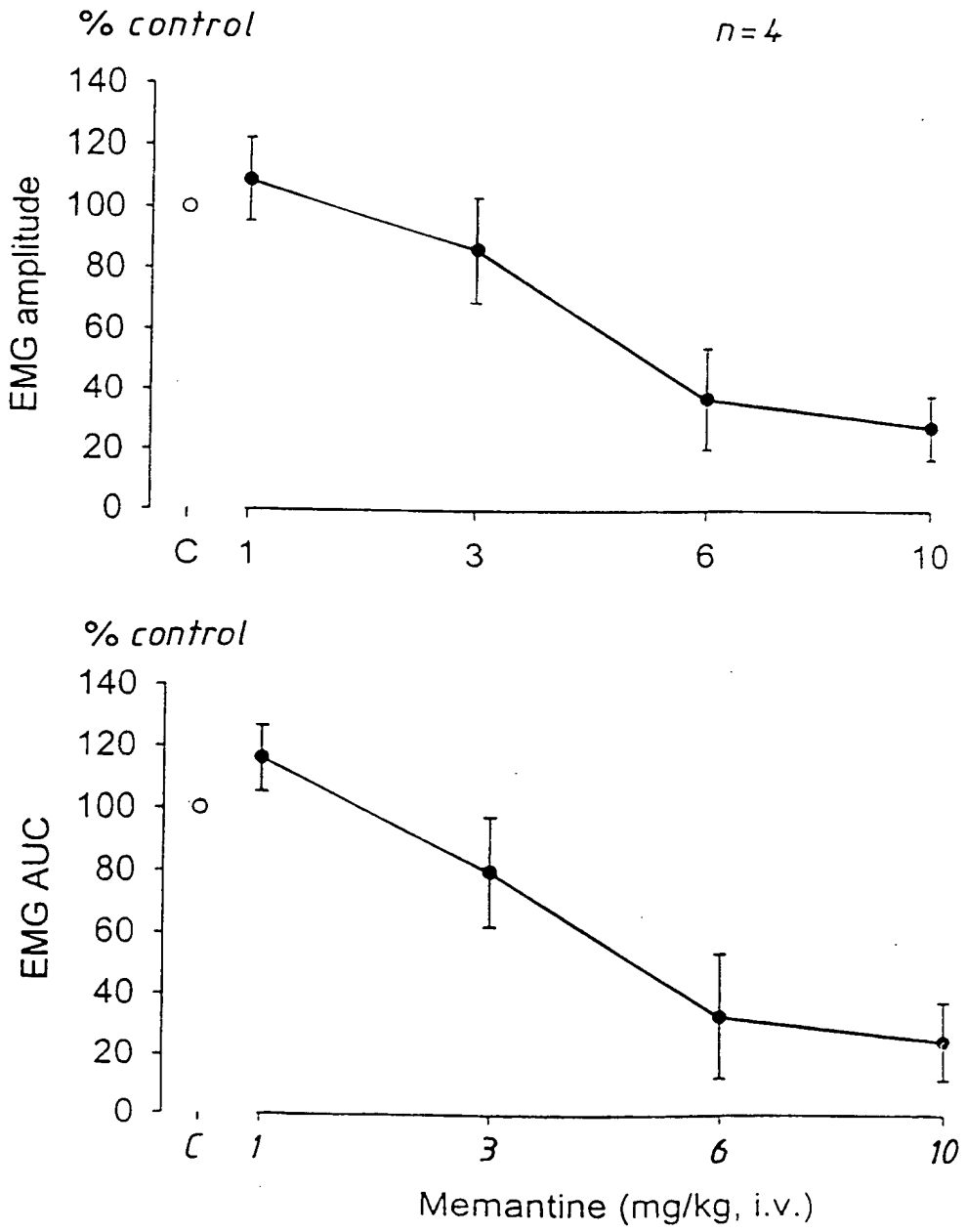
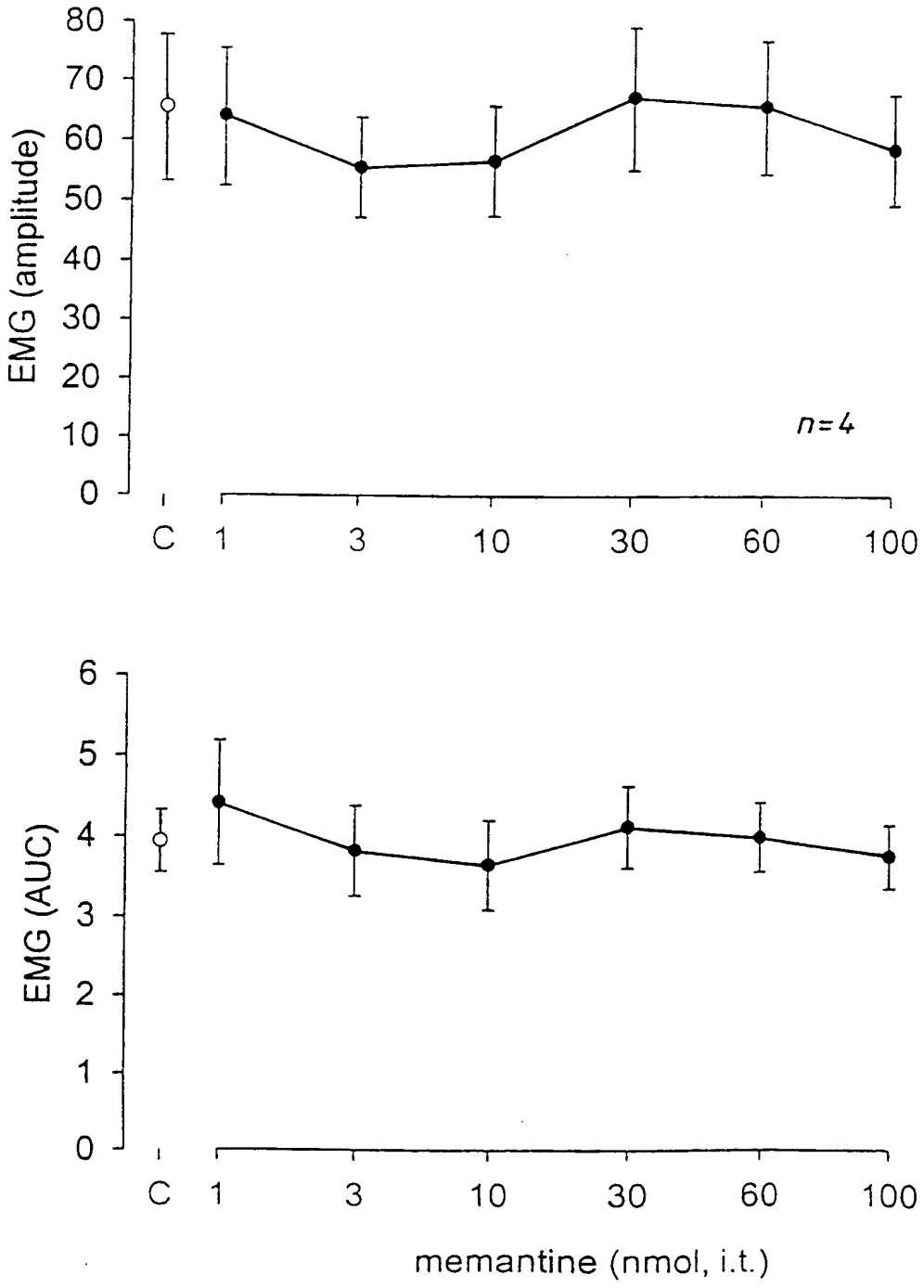

% control
n=4
EMG amplitude
140
120
100
80
60
40
20
0
C
1
3
6
10
% control
EMG AUC
140
120
100
80
60
40
20
0
C
1
3
6
10
Memantine (mg/kg, i.v.)

Fig. 2


EMG (amplitude)
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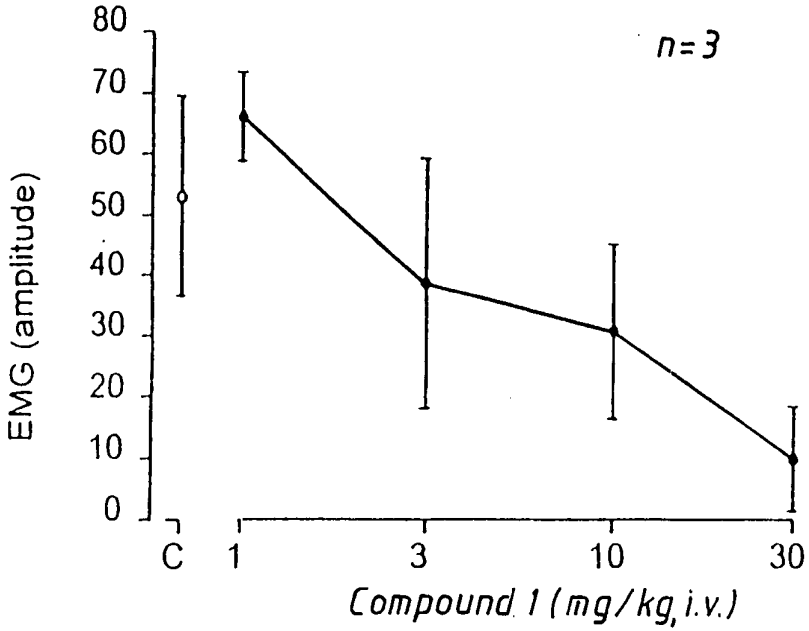
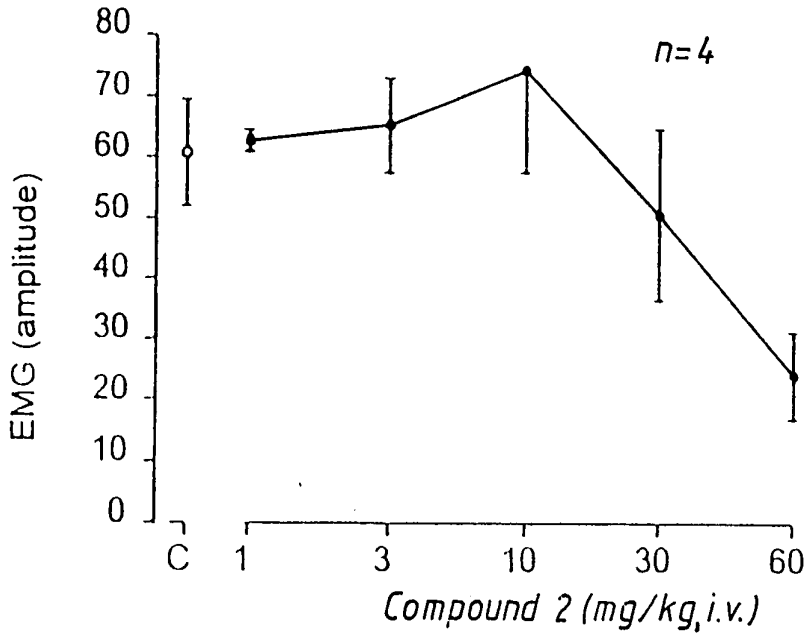
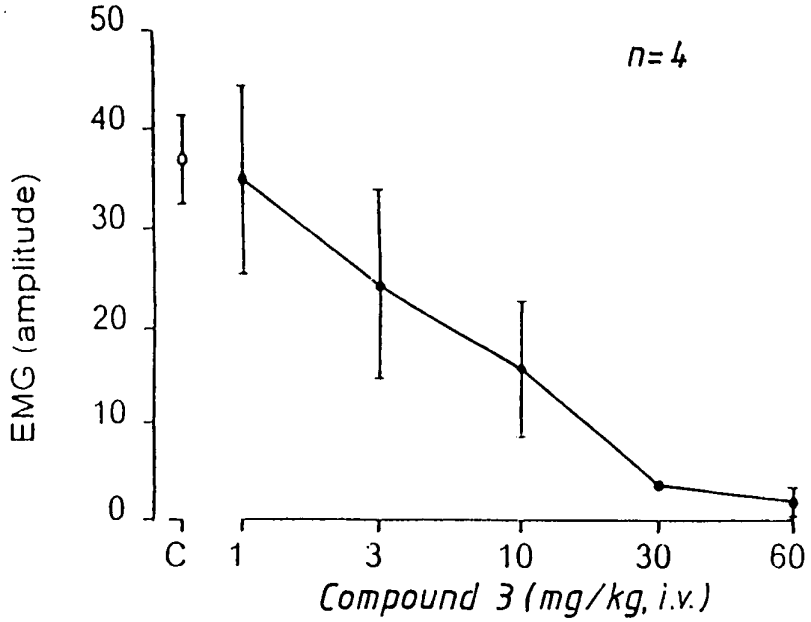
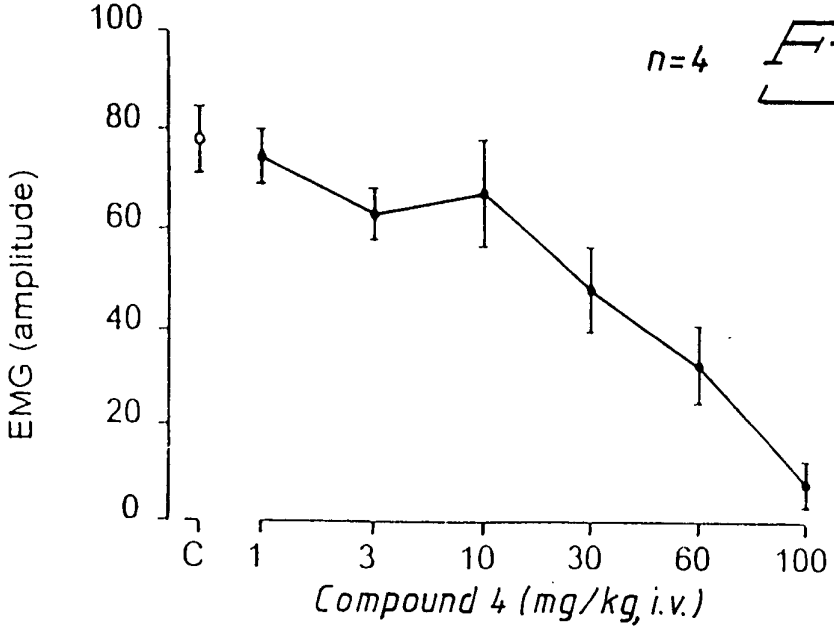
70
60
50
40
30
20
10
0
n=4
C
1
3
10
30
60
100
EMG (AUC)
6
5
4
3
2
1
0
C
1
3
10
30
60
100
memantine (nmol, i.t.)

Fig 3


n=3
EMG (amplitude)
0
10
20
30
40
50
60
70
80
C
1
3
10
30
Compound 1 (mg/kg, i.v.)


n=4
EMG (amplitude)
0
10
20
30
40
50
60
70
80
C
1
3
10
30
60
Compound 2 (mg/kg, i.v.)


n=4
EMG (amplitude)
0
10
20
30
40
50
C
1
3
10
30
60
Compound 3 (mg/kg, i.v.)


n=4
EMG (amplitude)
0
20
40
60
80
100
C
1
3
10
30
60
100
Compound 4 (mg/kg, i.v.)

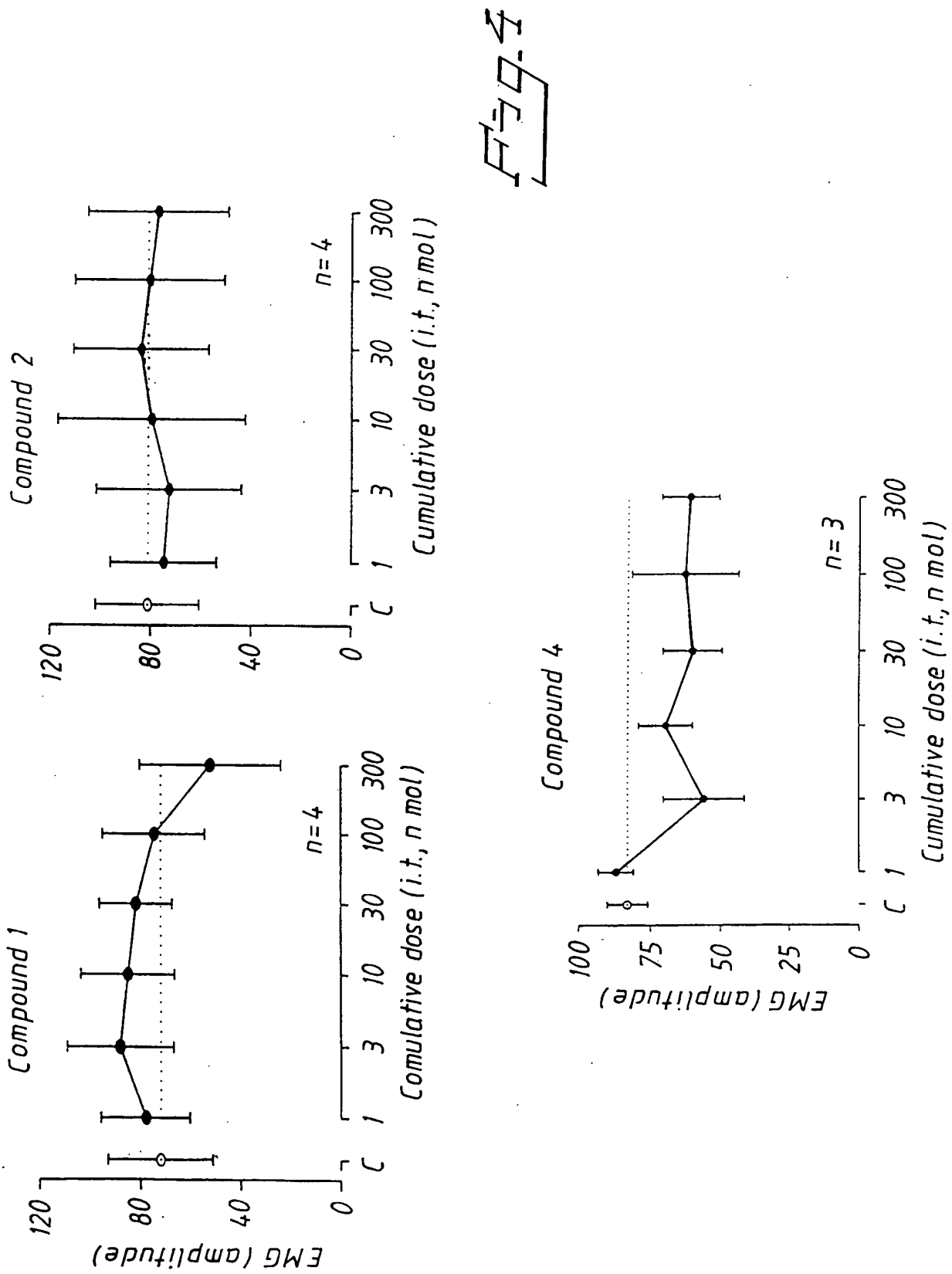

Compound 1
Compound 2
Compound 4
EMG (amplitude)
120
80
40
0
100
75
50
25
C
1
3
10
30
100
300
n=4
n=3
Cumulative dose (i.t., n mol)

Fig. 4

Fig. 5

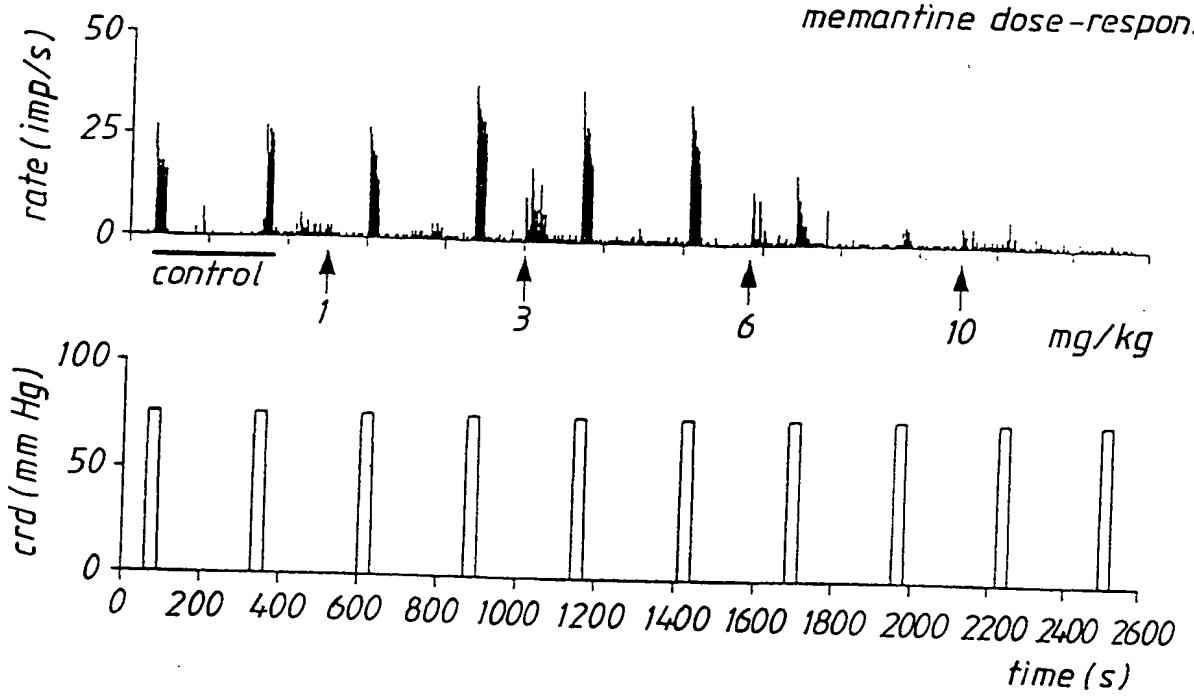
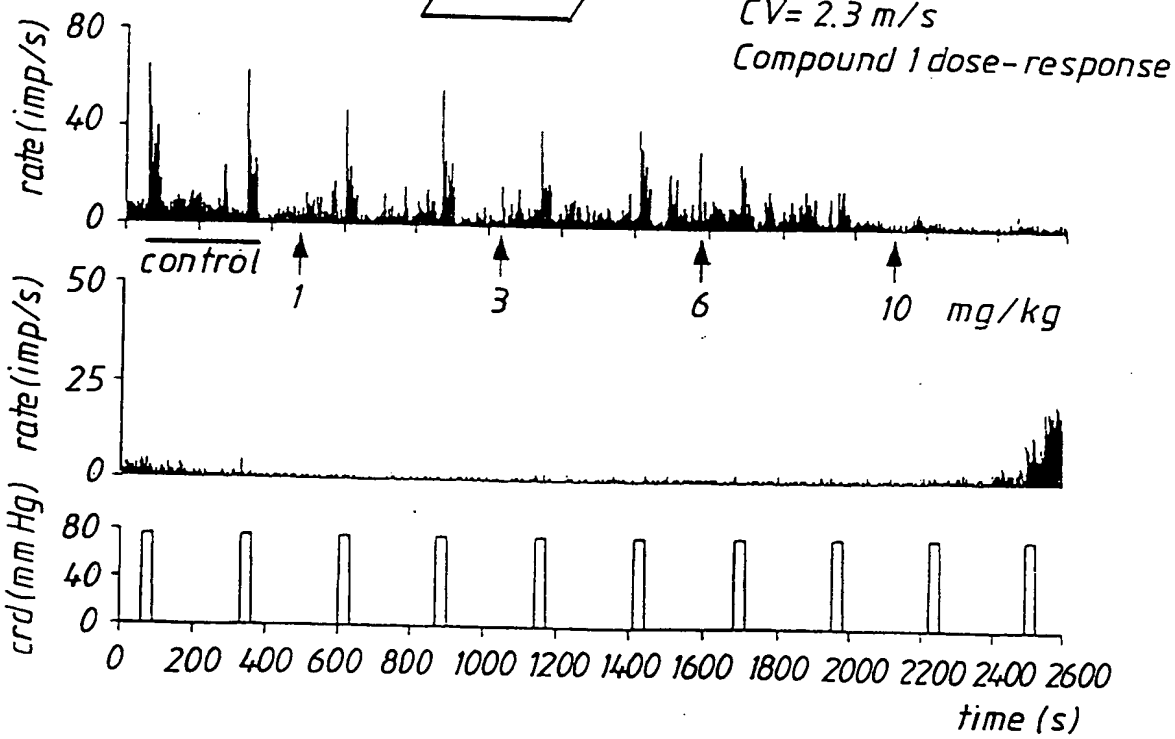

CV= 2m/s
memantine dose-response
rate (imp/s)
50
25
0
control
1
3
6
10
mg/kg
crd (mm Hg)
100
50
0
0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400 2600
time (s)

Fig. 6


CV= 2.3 m/s
Compound 1 dose-response
rate (imp/s)
80
40
0
control
1
3
6
10
mg/kg
rate (imp/s)
50
25
0
crd (mm Hg)
80
40
0
0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400 2600
time (s)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00702

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/165, A61K 31/13, A61K 31/41, A61K 31/44, A61K 31/495
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9709317 A2 (GLAXO GROUP LIMITED), 13 March 1997 (13.03.97) --	1-2
X	WO 9714415 A1 (F.H. FAULDING & CO. LIMITED), 24 April 1997 (24.04.97) -- --------	10-12

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the prionty date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 Sept 1999	07 -09- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00702

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☒ Claims Nos.: 1-2, 9, 10-11
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00702

BOX I 1.

Claim9 relates to a method of treatment of the human or animal body by surgery or by therapy practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.

BOX I 2.

Present claims 1-2, 9 and 10-11 relate to a compound/method defined by reference to desirable characteristic, namely NMDA antagonist activity or sodium antagonist activity. The claims cover all compounds having this characteristic, whereas the application provides support within the meaning of Article 6 PCT and /or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the applications so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been limited mainly to those compounds mentioned in the claims or the description.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/08/99

International application No.
PCT/SE 99/00702

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9709317 A2	13/03/97	AP 640 A	14/04/98
		AP 9600857 D	00/00/00
		AU 6986596 A	27/03/97
		BG 102342 A	30/09/98
		CA 2230362 A	13/03/97
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		GB 9518027 D	00/00/00
		HR 960399 A	30/04/98
		IL 123414 D	00/00/00
		NO 980923 A	04/05/98
		NZ 318390 A	25/02/99
		PL 325329 A	20/07/98
		SK 28598 A	09/09/98
WO 9714415 A1	24/04/97	AU 7207896 A	07/05/97
		AU PN605795 D	00/00/00
		EP 0858334 A	19/08/98